

ORIGINAL ARTICLE

Effect of mitochondrial-targeted antioxidants on glycaemic control, cardiovascular health, and oxidative stress in humans: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Aim: To investigate the effects of mitochondrial-targeted antioxidants (mitoAOXs) on glycaemic control, cardiovascular health, and oxidative stress outcomes in humans.

Materials and Methods: Randomized controlled trials investigating mitoAOX interventions in humans were searched for in databases (MEDLINE-PubMed, Scopus, EMBASE and Cochrane Library) and clinical trial registries up to 10 June 2021. The Cochrane Collaboration's tool for assessing risk of bias and Grading of Recommendations, Assessment, Development and Evaluations were used to assess trial quality and evidence certainty, respectively.

Results: Nineteen studies ($n = 884$ participants) using mitoAOXs (including Elamipretide, MitoQ and MitoTEMPO) were included in the systematic review. There were limited studies investigating the effects of mitoAOXs on glycaemic control; and outcomes and population groups in studies focusing on cardiovascular health were diverse. MitoAOXs significantly improved brachial flow-mediated dilation ($n = 3$ trials; standardized mean difference: 1.19, 95% CI: 0.28, 2.16; I^2 : 67%) with very low evidence certainty. No significant effects were found for any other glycaemic, cardiovascular or oxidative stress-related outcomes with mitoAOXs in quantitative analyses, with evidence certainty rated mostly as low. There was a lack of serious treatment-emergent adverse events with mitoAOXs, although subcutaneous injection of Elamipretide increased mild-moderate injection site-related events.

Conclusion: While short-term studies indicate that mitoAOXs are generally well tolerated, there is currently limited evidence to support the use of mitoAOXs in the management of glycaemic control and cardiovascular health. Review findings suggest that future research should focus on the effects of mitoAOXs on glycaemic control and endothelial function in target clinical population groups.

KEYWORDS

cardiovascular disease, glycaemic control, mitochondrial-targeted antioxidant, oxidative stress, reactive oxygen species

1 | INTRODUCTION

Mitochondria are a major producer of reactive oxygen species (ROS) in cells. Excess mitochondrial ROS has been implicated in the pathophysiology of various chronic diseases including Parkinson's disease, cardiovascular disease (CVD), type 2 diabetes, and cancer.¹⁻⁴ Antioxidant-based therapies have been used to target and reduce overproduction of ROS, although their efficacy overall appears heterogeneous for improving chronic disease-related outcomes.⁵⁻⁷ Moreover, antioxidants used in most studies are general and not targeted to specific sites within cells. Thus, they probably target multiple sources and sites of cellular ROS production. Given that mitochondrial-generated ROS have been pathologically implicated in many chronic diseases,¹⁻⁴ therapeutic approaches specifically targeting mitochondrial ROS may be effective and efficient for the management of ROS-related chronic diseases.⁸

Mitochondrial-targeted antioxidant (mitoAOX) therapies are designed specifically to allow an antioxidant agent to enter, accumulate and act within the mitochondria of cells. Among the various mitoAOX agents used in research studies are antioxidants with lipophilic cations attached (e.g. MitoQ, SKQ1, mito vitE and MitoTEMPO), liposome-encapsulated antioxidants (e.g. MITO-Porter-carried antioxidants), and peptide-based antioxidants targeting mitochondria (e.g. Elamipretide [a.k.a. SS-31 or MTP-131] and XJB-5-131).⁸

Growing evidence from preclinical studies has shown mitoAOXs to have beneficial effects on disease-related outcomes, including in models of CVD,^{9,10} neurological diseases^{11,12} and impaired glucose metabolism.¹²⁻¹⁵ There is also an increasing number of clinical trials that have been and/or are currently being conducted using specific mitoAOXs in patients with heart failure,¹⁶ mitochondrial genetic diseases¹⁷ and neurological diseases.¹⁸ While preclinical studies suggest a potential benefit of mitoAOXs for patients with impaired glucose metabolism, there is currently a lack of studies investigating the effects of mitoAOXs on glycaemic control and glucose metabolism in humans.

Overall, there is a lack of systematic reviews specifically focusing on the effects of mitoAOXs on chronic disease-related health outcomes. Thus, the aim of this systematic review was to undertake a systematic review to investigate the effects of mitoAOXs on glycaemic control, cardiovascular health, and oxidative stress in humans.

2 | METHODS

This systematic review includes randomized controlled trials (RCTs) involving human participants, and excludes non-randomized trials and

observational studies, trials that lack a placebo or control group, animal studies, and *in vitro* studies. Databases (MEDLINE-PubMed, Scopus, EMBASE and Cochrane Library) were searched up to and including 10 June 2021. Clinical trial registries (ClinicalTrials.gov, ANZCTR, EU Clinical Trial Register and ISRCTN) were also searched for unpublished studies with available results. No restrictions were placed on age or language of publication. One published study¹⁹ was later identified and added to the review. The search terms used are shown in **Table S1**. The systematic review was prospectively registered in the PROSPERO database (CRD42021253647).

The selection of studies was performed by two reviewers independently. First, potential studies were screened based on their titles and abstracts. The studies that were not ruled out in this procedure had their full texts evaluated. For all selected studies, the full text was sought, and their eligibility was double-checked. Studies with abstracts only (i.e. conference proceedings) that were relevant and informative of outcomes and that could be linked to clinical trial registry information were also included. Any disagreement between the two reviewers regarding the eligibility and inclusion of studies was adjudicated by a third reviewer. Articles meeting the inclusion and exclusion criteria were included in the systematic review.

The Cochrane Collaboration's tool for assessing the risk of bias in randomized trials was used to assess the quality of trials under domains of allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). Other biases were also evaluated based on the use of compliance-related measures and consideration of potentially confounding factors of diet and physical activity.

Data were extracted by two reviewers independently. A third reviewer adjudicated when there was a lack of consensus between the two reviewers. The following data were obtained from the studies: authors, publication year, study design, number of participants, health characteristics, gender, mean age, mean body mass index, duration of treatment, duration of wash-out (if a cross-over study), dose/dosage regimen of treatment, placebo/control used, losses per arm, adverse events, outcome measure means and standard deviations (SDs), and data to inform Cochrane bias domain assessments.

The direction of study outcomes (based on statistical significance) in relation to glycaemic control, cardiovascular health and oxidative stress were summarized and tabulated for individual studies. Additionally, quantitative estimates of effect sizes were determined when at least two studies included relevant quantitative data for a specific efficacy-related outcome using a random-effects model with DerSimonian-Laird methods in Review Manager software (Cochrane RevMan 5.3). Standardized mean differences with 95% confidence intervals (CIs) were used to represent the effect size for changes in the mitoAOX group

versus control group. Heterogeneity across studies was determined for specific outcomes using the I^2 statistic and chi-squared test, with I^2 more than 75% and/or chi-square P less than .1 denoting statistically significant heterogeneity.

In quantitative analyses, within-group post-treatment minus pre-treatment mean change was compared between mitoAOX and control groups for outcomes. For parallel design trials, mean changes provided were used or were calculated from pretreatment and post-treatment data. SDs of prepost changes were also used if provided or were calculated assuming a correlation coefficient of .7 if not provided.⁷ Cross-over trials were regarded similarly to parallel trials, with separate mitoAOX and control arms considered. For studies that did not provide pretreatment outcome values where post-treatment data were provided, only post-treatment data were used. For studies that did not provide post-treatment outcome values where pretreatment data were provided, pretreatment data were carried forward and assumed as post-treatment data. In a subsequent sensitivity analysis, exclusion of the latter studies had no meaningful impact on statistical findings for any outcome.

Small study effects were planned to be assessed using funnel plots and the Egger regression test if at least 10 studies reported on an outcome of interest, including at least one medium-size sample study.²⁰

Grading of evidence certainty was undertaken for outcomes with at least two studies reporting on them using GRADEpro GDT software (Evidence Prime, Inc, Hamilton, Canada), and involved assessing certainty of evidence based on concerns of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations, such as publication bias, effects size and potential confounding.²¹ Evidence was graded down a level when (a) statistical findings were inconsistent across individual Cochrane Risk of Bias domains when considering only 'low risk of bias' studies; (b) when heterogeneity across studies was statistically significant ($I^2 > 75\%$ and/or chi-squared $P < .1$); (c) when the outcome was a surrogate

rather than a patient-important outcome; and (d) if the sample size was small ($n < 200$).

3 | RESULTS

Nineteen studies ($n = 884$ participants) met the inclusion criteria and were included (Figure 1 and Table 1). The most common reasons for study exclusion were duplicate of the same study (same study/data published), wrong outcomes (study outcomes not relevant to the review), and wrong study design (non-RCTs). Of the included studies, 16 were full-text articles,^{16,17,19,23-28,30-35,37} two were abstracts that were linked to clinical trial registry information,^{22,29} and one was an unpublished study identified from a clinical trials registry.³⁶ Ten studies used Elamipretide as the mitoAOX agent,^{16,17,22-24,26,27,32,34,36} eight studies used MitoQ,^{19,25,29-31,33,35,37} and one study used MitoTEMPO.²⁸ Four studies included multiple mitoAOX treatment groups that used different mitoAOX doses.^{16,17,23,25} For these studies, mitoAOX group data were combined into a single group for quantitative analyses, with collective means and SDs determined according to recommended methods.³⁸ Fourteen studies included participants with specific health conditions^{16,17,22-30,32,34,36} and six studies included healthy participants.^{19,28,31,33,35,37} Thirteen studies involved chronic mitoAOX supplementation ranging from five to 84 days,^{16,17,19,22,25,27,29,31-33,35-37} while seven studies involved acute (<1 day) mitoAOX treatment.^{23,24,26,28,30,34,37} Individual study findings are summarized in Table 2.

Individual study quality was based on the number of 'low risk' Cochrane Risk of Bias domains (out of seven in total; Table 2). No studies were deemed to have any 'high risk' bias domains.

Most outcomes combined for quantitative analyses showed a lack of significant statistical heterogeneity across studies, although significant heterogeneity was reported for left atrial volume, right ventricular systolic pressure, brachial flow-mediated dilation and malondialdehyde (Table 3). GRADE evidence was largely of low evidence, certainty for

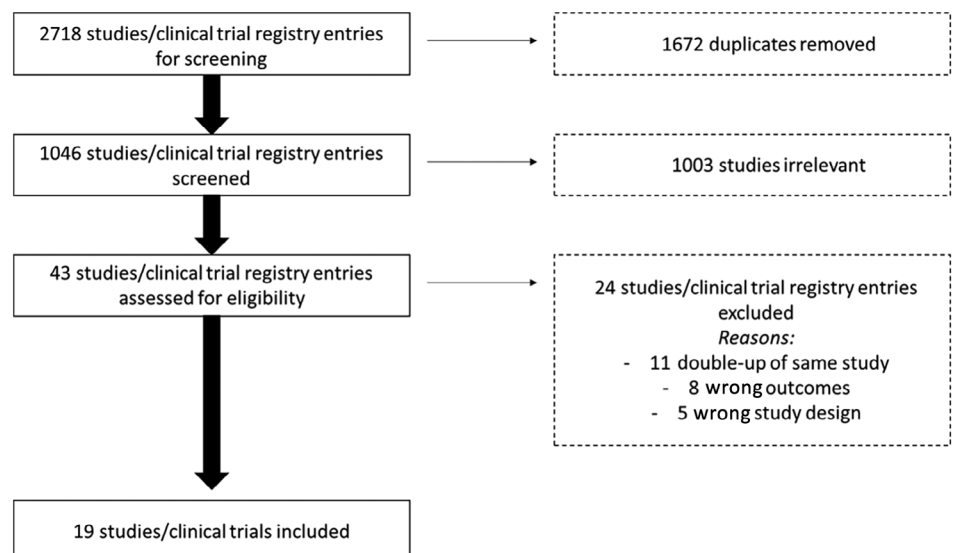


FIGURE 1 Selection of studies for the systematic review

TABLE 1 Studies included in the systematic review

References	Year	Parallel or cross-over	Control group	Duration (d)	Wash-out (d)	Blinding	AOX agent	AOX form	AOX dose × frequency per day	Total n	n male/female	Mean age (y)	Mean BMI (kg/m ²)	Healthy or health condition?	Study quality ^a
Broome et al. ¹⁹	2021	Cross-over	Placebo	28	42	Double	MitoQ	Tablets	20 mg × once	22	22/0	44	24.7	Healthy	5/7
Butler et al. ¹⁶	2020	Parallel	Placebo	28	N/A	Double	Elamipretide	S.C. injection	4 mg or 40 mg × once	71	54/17	64.8	28.4	Heart failure with reduced ejection fraction	6/7
Cleland et al. ²²	2019	Parallel	Placebo	Up to 7	N/A	Double	Elamipretide	I.V. injection	20 mg × once	306	239/67	70.3	N/A	Heart failure with an LVEF = 40% within 48 h of an admission for worsening peripheral oedema	1/7
Daubert et al. ²³	2017	Parallel	Placebo	4 h	N/A	Double	Elamipretide	I.V. infusion	0.005 or 0.05 or 0.25 mg/kg/h	36	28/8	62	26	Heart failure with reduced ejection fraction (ejection fraction ≤ 35%)	4/7
Eirin et al. ²⁴	2018	Parallel	Placebo	30 min pre- to 2.5 h post-PTRA	N/A	Double	Elamipretide	I.V. infusion	0.05 mg/kg/h	14	7/7	67.7	30.5	Renovascular hypertension patients undergoing PTRA	0/7
Gane et al. ²⁵	2010	Parallel	Placebo	28	N/A	Double	MitoQ	Tablets	40 mg or 80 mg × once	30	19/11	47.7	27.1	Patients with document history of chronic HCV infection	5/7
Gibson et al. ²⁶	2016	Parallel	Placebo	15-60 min pre-PCI and for 1 h following reperfusion	N/A	Double	Elamipretide	I.V. injection	0.05 mg/kg/h	118	85/33	60.1	N/A	First-time anterior STEMI subjects undergoing primary PCI for a proximal or mid left anterior descending artery occlusion	2/7
Karaa et al. ²⁷	2020	Cross-over	Placebo	28	28	Double	Elamipretide	S.C. injection	40 mg × once	30	5/25	45.3	24.1	Genetically confirmed primary mitochondrial myopathy	5/7
Karaa et al. ¹⁷	2018	Parallel	Placebo	2 h per day for 5 consecutive days	N/A	Double	Elamipretide	I.V. infusion	0.01 or 0.1 or 0.25 mg/kg/h	36	6/30	43	23	Genetically confirmed primary mitochondrial myopathy	5/7
Kirkman et al. ²⁸	2018	Cross-over	Placebo	Acute infusion	N/A	Unclear	MitoTempo	I.V. infusion	1 mM	11	6/5	58	24	Healthy	2/7
Kirkman et al. ²⁹	2020	Parallel	Placebo	28	N/A	Double	MitoQ	Capsules	20 mg × once	18	n.s.	62	N/A	Stage 3-5 CKD	2/7 ^b
Park et al. ³⁰	2020	Cross-over	Placebo	Acute ingestion	14	Double	MitoQ	Capsules	80 mg × once	11	5/6	66.1	30	Peripheral artery disease	3/7

TABLE 1 (Continued)

References	Year	Parallel or cross-over	Control group	Duration (d)	Wash-out (d)	Blinding	AOX agent	AOX form	AOX dose × frequency per day	Total n	n male/female	Mean age (y)	Mean BMI (kg/m ²)	Healthy or health condition?	Study quality ^a
Pham et al. ³¹	2020	Cross-over	Co-enzyme Q	42	42	Double	MitoQ	Capsules	20 × mg × once	20	20/0	50.8	26.6	Healthy	5/7
Reid Thompson et al. ³²	2021	Cross-over	Placebo	84	28	Double	Elamipretide	S.C. injection	40 mg × once	12	12/0	19.5	17.6	Genetically confirmed Barth syndrome	5/7
Rossmann et al. ³³	2018	Cross-over	Placebo	42	0	Double	MitoQ	Capsules	20 mg × once	24	9/11	68	23	Healthy	7/7
Saad et al. ³⁴	2017	Parallel	Placebo	30 min prior to PTRAs until 3 h post	N/A	Double	Elamipretide	I.V. infusion	0.05 mg/kg/h	14	7/7	70.0	30.9	Patients with severe atherosclerotic renal artery stenosis scheduled for PTRAs	4/7
Shill et al. ³⁵	2016	Parallel	Placebo	21	N/A	Double	MitoQ	Capsules	10 mg × once	20	20/0	22.1	26.9	Healthy	4/7
Stealth biotherapeutics Inc. ³⁶	2021	Parallel	Placebo	28	N/A	Double	Elamipretide	S.C. injection	40 mg × once	47	17/30	70.5	N/A	Heart failure with preserved ejection fraction	3/7 ^b
Williamson et al. ³⁷	2020	Parallel	Placebo	Acute ingestion 1 h pre-exercise and 21 d	N/A	Double	MitoQ	Capsules	20 mg × once	24	24/0	25	26.6	Healthy	3/7

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; HCV, hepatitis C virus; I.V., intravenous; LVEF, left ventricular ejection fraction; N/A, not applicable; n.s., not specified; PCI, percutaneous coronary intervention; PTRAs, percutaneous transluminal renal angioplasty; S.C., subcutaneous; STEMI, ST-elevation myocardial infarction.

^aStudy quality based on no. of Cochrane low risk-of-bias domains.

^bStudy quality based only on abstract/clinical trial registry data.

TABLE 2 Summary of direction of glycaemic control, cardiovascular health, and oxidative stress impacts in included studies (mitoAOX vs. control)

MitoAOX agent	Health condition	Sample size (n)	Acute/chronic (n days)	Dosage	Glycaemic control outcomes	Cardiovascular health-related outcomes					Oxidative stress-related outcomes		Reference	
						Blood pressure	Cardiac measure	Marker of cardiac function	Endothelial/vascular function	Functional/patient-important measure	Lipids	stress-related outcomes		
Studies in patients with health conditions	Heart failure	71	Chronic (28 d)	4 mg × once daily	n/a	n/a	↔ ^a , ↓ ^b	↔ ^c	n/a	↔ ^c	n/a	n/a	16	
	Heart failure	306	Chronic (7 d)	40 mg × once daily	n/a	n/a	↔ ^c	↔ ^c	n/a	↔ ^c	n/a	n/a	22	
	Heart failure	36	Acute	20 mg × once daily	n/a	n/a	↔ ^c	↔ ^c	n/a	n/a	↔ ^c	n/a	23	
	Renovascular hypertension		14	Acute	0.005 mg/kg/h	n/a	n/a	↔ ^c	↔ ^c	n/a	n/a	↔ ^c	n/a	24
			118	Acute	0.05 mg/kg/h	n/a	n/a	↔ ^a , ↓ ^d	↔ ^c	n/a	↔ ^c	n/a	↔ ^c	26
			30	Chronic (28 d)	40 mg × once daily	n/a	n/a	↔ ^c	n/a	n/a	↓ ^g	n/a	↔ ^c	27
	Primary mitochondrial myopathies		36	Chronic (2 h/d for 5 d)	0.01 mg/kg/h	n/a	n/a	n/a	n/a	n/a	↔ ^c	n/a	↔ ^c	17
			12	Chronic (84 d)	0.1 mg/kg/h	n/a	n/a	n/a	n/a	n/a	↔ ^c	n/a	↔ ^c	32
			14	Acute	0.25 mg/kg/h	n/a	n/a	n/a	n/a	n/a	↑ ^h	n/a	↔ ^c	34
	Severe atherosclerotic renal artery stenosis		14	Chronic (84 d)	40 mg × once daily	n/a	n/a	↓ ^f	n/a	n/a	n/a	n/a	n/a	36
		47	Chronic (28 d)	0.05 mg/kg/h	n/a	n/a	n/a	↔ ^c	n/a	↔ ^c	n/a	n/a	25	
		30	Chronic (28 d)	40 mg × once daily	n/a	n/a	n/a	n/a	n/a	n/a	↔ ^c	n/a	29	
Chronic HCV infection		18	Chronic (28 d)	80 mg × once daily	n/a	n/a	↔ ^c	n/a	n/a	n/a	↔ ^c	n/a	30	
		11	Acute	20 mg × once daily	n/a	n/a	↔ ^c	n/a	↑ ^k	↑ ^l	n/a	↔ ^a , ↑ ^m		

TABLE 2 (Continued)

MitoAOX agent	Health condition	Sample size (n)	Acute/chronic (n days)	Dosage	Glycaemic control outcomes	Cardiovascular health-related outcomes					Oxidative stress-related outcomes		Reference
						Blood pressure	Cardiac measure	Marker of cardiac function	Endothelial/vascular function	Functional/patient-important measure	Lipids	stress-related outcomes	
MitoTEMPO	CKD	20	Acute	1 mM	n/a	n/a	n/a	↑ ⁿ	n/a	n/a	n/a	n/a	28
Studies in healthy participants	MitoQ	22	Chronic (28 d)	20 mg × once daily	↔ ^c	n/a	n/a	n/a	↔ ^c	↔ ^c	↔ ^c	↓ ^o	19
		20	Chronic (42 d)	20 × mg × once daily	↔ ^c	n/a	↔ ^c	n/a	n/a	↔ ^c	↔ ^c	↔ ^a , ↓ ^p	31
		20	Chronic (42 d)	20 × mg × once daily	↔ ^c	n/a	↔ ^c	↑ ^q	n/a	↔ ^c	↔ ^c	↓ ^r	33
		20	Chronic (21 d)	10 × mg × once daily	n/a	n/a	n/a	n/a	↔ ^c	n/a	↔ ^c	↔ ^c	35
		24	Acute	20 mg	n/a	n/a	n/a	n/a	n/a	n/a	n/a	↔ ^c	37
		24	Chronic (21 d)	20 × mg once daily	n/a	n/a	n/a	n/a	n/a	n/a	n/a	↔ ^s	28
MitoTEMPO	-	11	Acute	1 mM	n/a	n/a	n/a	↔ ^c	n/a	n/a	n/a	n/a	28

Note: ↔, no statistically significant change in measured outcomes; ↑, statistically significant increase in measured outcomes; ↓, statistically significant decrease in measured outcomes.

Abbreviations: CKD, chronic kidney disease; FMD, flow-mediated dilation; HCV, hepatitis C virus; mitoAOX, mitochondrial-targeted antioxidant; n/a, not assessed; Neuro-QoL, Quality of Life in Neurological Disorders; PMMSA, Primary Mitochondrial Myopathy Symptom Assessment; RCT, randomized controlled trial; ROS, reactive oxygen species; STEMI, ST-elevation myocardial infarction.

^aNo changes for most outcomes assessed, but with exceptions.

^bLeft atrial volume.

^cNo changes for all outcomes assessed.

^dRight systolic ventricle pressure.

^eLeft ventricle end systolic volume and left ventricle end diastolic volume.

^fSystolic blood pressure change within mitoAOX group only.

^gPMMSA Total Fatigue score, PMMSA Fatigue During Activities score, patient global assessment and Neuro-QoL Fatigue Short Form.

^h6-min walk test distance, when using an adjusted statistical model.

ⁱNo changes in part 1 of study (RCT), but improvements in numerous functional/patient-important outcomes in part 2 of study (non-controlled, open-label trial).

^jCentral pressure waveforms (forward) and brachial FMD.

^kBrachial FMD and popliteal FMD.

^lMaximal walking distance, maximum walking time and time to onset of claudication.

^mPlasma superoxide dismutase.

ⁿPlateau phase of cutaneous vascular conductance.

^oPlasma F₂-Isoprostanes.

^pSkeletal muscle H₂O₂ in Complex I and Complex II leak after addition of oligomycin (Leak_o state) within mitoAOX group only.

^qBrachial FMD, FMD associated with amelioration of mitochondrial ROS-related suppression of endothelial function (assessed as the increase in FMD with acute, supratherapeutic MitoQ [160 mg] and carotid-femoral pulse-wave velocity in participants with elevated baseline carotid-femoral pulse wave velocity levels.

^rPlasma LDL oxidation.

^sNo changes in oxidative stress markers/antioxidants, although exercise-induced nuclear and mitochondrial DNA damage was decreased in lymphocytes and muscle following mitoAOX supplementation.

TABLE 3 Quantitative syntheses of outcomes (with at least two studies) for mitoAOX versus control

Outcome	Studies (n)	Participants (n)	SMD	95% CI	P value	I ² (P value)	GRADE
Fasting glucose	2	71	0.24	−0.22, 0.71	.31	0% (.59)	LOW ^{a,b}
Systolic brachial BP	7	175	−0.19	−0.50, 0.13	.24	0% (.78)	LOW ^{a,b}
Diastolic brachial BP	4	115	−0.23	−0.59, 0.14	.23	0% (.79)	LOW ^{a,b}
Systolic central BP	2	40	−0.32	−0.95, 0.30	.31	0% (.99)	LOW ^{a,b}
LVESV	3	217	0.12	−0.16, 0.40	.39	0% (1.00)	LOW ^{a,b}
LVEDV	3	217	0.05	−0.23, 0.33	.71	0% (.90)	LOW ^{a,b}
LVEF	3	217	−0.08	−0.36, 0.20	.57	0% (.66)	LOW ^{a,b}
Left atrial volume	2	99	−0.13	−1.27, 1.01	.82	74% (.05)	VERY LOW ^{a,b,c,d}
Left ventricle mass	2	189	0.07	−0.23, 0.36	.66	0% (.75)	LOW ^{a,b}
RV fractional area change	2	99	−0.12	−0.57, 0.33	.60	0% (.74)	LOW ^{a,b}
RV systolic pressure	2	91	−0.63	−2.97, 1.71	.60	91% (.0006)	VERY LOW ^{a,b,c,d}
E/e'	2	118	0.01	−0.36, 0.38	.96	0% (.93)	LOW ^{a,b}
LVGLS	3	138	0.16	−0.28, 0.61	.47	28% (.25)	LOW ^{a,b}
Heart rate	3	88	0.06	−0.40, 0.52	.79	0% (.78)	LOW ^{a,b}
NT-proBNP	4	452	0.01	−0.18, 0.19	.96	0% (.91)	MODERATE ^a
hs-CRP	3	107	0.03	−0.38, 0.43	.90	0% (.77)	LOW ^{a,b}
Brachial FMD	3	80	1.19	0.28, 2.16	.01	67% (.05)	VERY LOW ^{a,b,c,d}
CFPWV	2	62	−0.02	−0.52, 0.48	.93	0% (.97)	LOW ^{a,b}
6-min walk test distance	4	214	0.06	−0.22, 0.34	.69	0% (.75)	MODERATE ^a
Triglycerides	2	71	0.23	−0.24, 0.69	.34	0% (.72)	LOW ^{a,b}
MDA	3	81	−0.53	−1.43, 0.37	.25	73% (.03)	VERY LOW ^{a,b,c}
F ₂ -Isoprostanes	3	107	−0.01	−0.58, 0.51	.98	45% (.16)	LOW ^{a,b}

Abbreviations: BP, blood pressure; CFPWV, carotid-to-femoral pulse wave velocity; E/e', ratio between early mitral inflow velocity and mitral annular early diastolic velocity; FMD, flow-mediated dilation; hs-CRP, high-sensitivity C-reactive protein; LVEDV, left ventricle end diastolic volume; LVEF, left ventricle ejection fraction; LVESV, left ventricle end systolic volume; LVGLS, left ventricle global longitudinal strain; MDA, malondialdehyde; mitoAOX, mitochondrial-targeted antioxidant; NT-proBNP, N-terminal-pro hormone BNP; RV, right ventricle; SMD, standardized mean difference.

^aSurrogate measure, not patient-important outcome.

^bLess than 200 participants per arm.

^cI²>75% or chi square $P < .1$.

^dInconsistent significance when considering risk of bias domains with low risk only across all domains.

outcomes (Table 3). There were insufficient studies included in the review to investigate small study effects.

3.1 | Glycaemic control outcomes

Two studies reported quantitatively on glycaemic control-related outcomes following mitoAOX supplementation, both in healthy males^{19,31} (Table 2). In one study,³¹ no effects of treatment were found for HbA1c, fasting glucose, fasting insulin, or Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) after 6 weeks of supplementation with 20 mg MitoQ per day. In another study,¹⁹ pre, during and postmoderate-intensity exercise plasma glucose concentrations were unaffected in trained male cyclists after 4 weeks of supplementation with 20 mg MitoQ per day. In quantitative analyses of glycaemic-related outcomes that were reported in at least two

studies, no effect was found for fasting glucose in response to MitoQ supplementation (Table 4 and Figure S1).

3.2 | Cardiovascular health outcomes

Cardiac measures such as left ventricle end systolic volume (LVESV), left ventricle end diastolic volume (LVEDV), and LV ejection fraction (LVEF) were unchanged after Elamipretide in some studies, although a dose-related improvement in LVESV and LVEDV was reported in one study involving an acute infusion of Elamipretide in heart failure patients with reduced ejection fraction²³ (Table 2). Similarly, cardiac function markers such as left ventricular filling pressure (E/e'), left ventricular global longitudinal strain (LVGLS, a measure of systolic function), N-terminal pro b-type natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein did not significantly change with mitoAOX treatments. Functional-related outcomes were also largely

TABLE 4 Documented adverse events and safety-related outcomes in included studies

Study	Treatment	mitoAOX group	Control group
Broome et al. ¹⁹	MitoQ	No unfavourable or AEs reported	No unfavourable or AEs reported
Butler et al. ¹⁶	Elamipretide	4 mg dose: n = 9 (41%) AEs, n = 5 (23%) TEAEs (n = 1 [4%] injection-site reactions), n = 0 SAEs, n = 0 serious TEAEs, n = 0 deaths, n = 1 (4.5%) discontinuation because of TEAEs 40 mg dose: n = 16 (64%) AEs, n = 7 (28%) TEAEs (n = 6 [24%] injection-site reactions, n = 1 (4%) SAE, n = 1 (4%) serious TEAEs, n = 0 deaths, n = 0 discontinuation because of TEAEs	n = 10 (42%) AEs, n = 0 TEAEs, n = 0 SAEs, n = 0 serious TEAEs, n = 0 all deaths, n = 0 discontinuation because of TEAEs Rates of any study drug-related events similar across all groups
Cleland et al. ²²	Elamipretide	Within 40 d of randomization, n = 10 patients were rehospitalized for heart failure or had a cardiovascular death. Mean length of hospitalization admission: 10 (8-12) d eGFR change: +1 (-5, 7) ml/min/1.73m ²	Within 40 d of randomization, n = 16 patients were rehospitalized for heart failure or had a cardiovascular death. Mean length of hospitalization admission: 9 (8-10) d Differences in outcomes not significantly different between groups
Daubert et al. ²³	Elamipretide	0.005 mg/kg/h dose: n = 1 (12%) AEs, n = 0 SAEs, n = 0 discontinuation because of AEs 0.05 mg/kg/h dose: n = 2 (25%) AEs, n = 0 SAEs, n = 1 discontinuation because of AEs 0.25 mg/kg/h dose: n = 0 AEs, n = 0 SAEs, n = 0 discontinuation because of AEs	n = 0 AEs, n = 0 SAEs, n = 0 discontinuation because of AEs Differences in outcomes not significantly different between groups
Eirin et al. ²⁴	Elamipretide	eGFR significantly increased (+5.83 ± 2.64 ml/min/1.73m ²)	eGFR did not change significantly (+1.86 ± 3.63 ml/min/1.73m ²)
Gane et al. ²⁵	MitoQ	40 mg/d dose: n = 29 AEs (n = 10 gastrointestinal disorder - mostly nausea, vomiting, n = 8 nervous system disorder), n = 0 SAEs, n = 1 discontinuation because of AEs ALT and AST decreased significantly versus placebo 80 mg/d dose: n = 21 AEs (n = 8 gastrointestinal disorder, n = 4 nervous system disorder), n = 0 SAEs, n = 0 discontinuation because of AEs. ALT decreased significantly versus placebo	n = 19 AEs (n = 1 gastrointestinal disorder, n = 5 nervous system disorder), n = 0 SAEs, n = 0 discontinuation because of AEs Except for higher gastrointestinal disorder events with MitoQ, no significant differences in the incidence of AEs were observed between groups
Gibson et al. ²⁶	Elamipretide	In primary cohort: n = 8 (13.8%) had CHF events <24 h post-PCI, n = 7 (12.1%) had any of: death, new-onset CHF or CHF rehospitalization at 30 d, n = 5 (8.6%) had any of: death, new-onset CHF or CHF rehospitalization at 6 mo In safety cohort: n = 20 (13.3%) had serious TEAEs, n = 2 (1.3%) had new MI, n = 37 (24.7%) had CHF Rise in serum creatinine with Elamipretide (+1 µmol/L) significantly lower versus placebo (+3.7 µmol/L)	In primary cohort: n = 15 (25%) had CHF events <24 h post PCI, n = 5 (8.3%) had any of: death, new-onset CHF or CHF rehospitalization at 30 d, n = 3 (5%) had any of: death, new-onset CHF or CHF rehospitalization at 6 mo In safety cohort: n = 14 (9.5%) had serious TEAEs, n = 6 (4.1%) had new MI, n = 41 (27%) had CHF Apart from creatinine, no significant difference in outcomes between groups
Karaa et al. ¹⁷	Elamipretide	n = 62 (total) AEs (including n = 48 injection-site AEs), n = 0 SAEs, n = 1 discontinuation because of AE	n = 18 (total) AEs (including n = 5 injection-site AEs), n = 0 SAEs, n = 0 discontinuation because of AE
Karaa et al. ²⁷	Elamipretide	0.01 mg/kg/h dose: n = 7 (77.8%) AEs (n = 1 [11.1%] gastrointestinal disorder, n = 3 [33.3%] nervous system disorder), n = 0 SAEs, n = 0 deaths, n = 0 discontinuation because of AEs 0.1 mg/kg/h dose: n = 7 (77.8%) AEs (n = 3 [33.3%] gastrointestinal disorder, n = 2 [22.2%] nervous system disorder), n = 0 SAEs, n = 0 deaths, n = 0 discontinuation because of AEs 0.25 mg/kg/h dose: n = 5 (55.6%) AEs (n = 0 gastrointestinal disorder, n = 2 [22.2%] nervous system disorder), n = 0 SAEs, n = 0 deaths, n = 0 discontinuation because of AEs	n = 5 (55.6%) AEs (n = 2 [22.2%] gastrointestinal disorder, n = 2 [22.2%] nervous system disorder), n = 0 SAEs, n = 0 deaths, n = 0 discontinuation because of AEs No effect of treatments on ECG or blood chemistry measures

(Continues)

TABLE 4 (Continued)

Study	Treatment	mitoAOX group	Control group
Park et al. ³⁰	MitoQ	No unfavourable or AEs reported	No unfavourable or AEs reported
Pham et al. ³¹	MitoQ	No unfavourable or AEs reported	No unfavourable or AEs reported
Reid Thompson et al. ³²	Elamipretide	n = 74 (total) TEAEs across 12/12 participants reported (n = 46 injection site-related events in 12/12 participants, n = 1 [8.3%] gastrointestinal disorders, n = 3 [25%] nervous system disorders)	n = 47 (total) TEAEs across 10/12 participants reported (n = 13 injection site-related events in 8/12 participants, n = 4 [33.3%] gastrointestinal disorders, n = 5 [41.7%] nervous system disorders)
Rossmann et al. ³³	MitoQ	n = 1 (total) TEAEs (n = 1 gastrointestinal disorder), n = 0 SAEs, n = 0 discontinuation because of AEs	n = 3 (total) TEAEs (n = 3 gastrointestinal disorder), n = 0 SAEs, n = 0 discontinuation because of AEs A further n = 3 (total) TEAEs (n = 3 gastrointestinal disorder) were reported following acute administration of 160 mg MitoQ, but unclear which group this occurred in
Saad et al. ³⁴	Elamipretide	No unfavourable or AEs reported eGFR significantly increased (+5.8 ± 11.1 ml/min/1.73m ²)	No unfavourable or AEs reported eGFR did not significantly change (+2.6 ± 7.8 ml/min/1.73m ²)
Shill et al. ³⁵	MitoQ	No AEs reported, including during exercise	No AEs reported, including during exercise
Stealth biotherapeutics Inc. ³⁶	Elamipretide	n = 14 (60.9%) AEs (n = 20 [total] injection site-related events, n = 0 nervous system disorders), n = 0 SAEs, n = 12 (52.2%) TEAEs, n = 1 severe TEAE, n = 0 deaths, n = 0 discontinuation because of AEs	n = 7 (29.2%) AEs (n = 2 [total] injection site-related events, n = 1 [4.17%] nervous system disorders), n = 1 (4.17%) SAEs (n = 1 acute MI causing death), n = 2 (8.3%) TEAEs, n = 0 severe TEAE, n = 1 deaths, n = 1 discontinuation because of AEs
Williamson et al. ³⁷	MitoQ	No unfavourable or AEs reported	No unfavourable or AEs reported

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CHF, congestive heart failure; ECG, echocardiogram; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; mitoAOX, mitochondrial-targeted antioxidant; PCI, percutaneous coronary intervention; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

unchanged with mitoAOX treatments, although an Elamipretide dose-related improvement in 6-minute walk test performance was reported in a study involving 5 days of Elamipretide infusions in patients with genetically confirmed primary mitochondrial myopathies when considering a corrected statistical model.¹⁷

Patient-important outcomes including quality of life outcomes on the Kansas City Cardiomyopathy questionnaire and Barth Syndrome Symptom Assessment (a scale reporting on symptoms in patients with Barth Syndrome), all-cause mortality, CVD-related mortality, incidence of new congestive heart failure, rehospitalization because of heart failure, and duration of hospitalization remained unchanged after Elamipretide treatment.^{16,17,22,26,32,36} However, in one study Elamipretide supplementation (40 mg/d for 28 days) significantly improved the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA) total fatigue score, PMMSA Fatigue During Activities score, Patient global assessment and Quality of Life in Neurological Disorders Fatigue Form in patients with primary mitochondrial myopathies.²⁷ In another study in patients with mitochondrial myopathies, Elamipretide supplementation (dosages of 0.02-0.5 mg/kg for 5 days) had no effect on outcomes in a Daily Symptoms Questionnaire or modified newcastle mitochondrial disease adult scale (NMDAS) questionnaire (focusing on quality of life and symptoms in patients with mitochondrial diseases).¹⁷

Elamipretide treatment improved systolic brachial blood pressure in two studies in patients with atherosclerosis-related impaired renal blood flow.^{24,34} Acute MitoQ supplementation (80 mg) improved brachial and popliteal flow-mediated dilation (FMD), maximum walking time, maximum walking distance, and time to onset of claudication in patients with peripheral artery disease (PAD) in one study.³⁰ Chronic MitoQ supplementation (20 mg/d) improved brachial FMD in one study involving healthy older participants³³; and improved brachial FMD and central pressure waveforms in participants with chronic kidney disease²⁹ (Table 2). MitoTEMPO infusion significantly increased the plateau phase of cutaneous vascular conductance in chronic kidney disease patients to levels observed in healthy controls in one study²⁸ (Table 2).

Quantitative analyses conducted for cardiovascular health-related outcomes reported in at least two studies found a statistically significant lowering effect of mitoAOX treatments on brachial FMD, but not on any other cardiovascular health-related outcome (Table 3 and Figures S2-S4).

3.3 | Oxidative stress outcomes

Some studies using MitoQ found improvements in markers of oxidative stress (Table 2). One study in healthy older participants reported

an association between the improvement in brachial FMD with MitoQ supplementation and the amelioration of mitochondrial ROS-related suppression of endothelial function.³³ In that study, a 62% improvement in brachial FMD was elicited by a single dose of MitoQ (160 mg) given after the placebo phase, while only a 7% improvement was found with acute MitoQ supplementation after the chronic MitoQ phase (20 mg MitoQ/d). In the same study, plasma LDL oxidation significantly decreased after supplementation with 20 mg MitoQ per day for 6 weeks. Another study in healthy participants found a significant decrease in skeletal muscle H₂O₂ concentration in Complex I and complex II leak after addition of oligomycin (leak_o state) following supplementation with 20 mg MitoQ per day for 6 weeks³¹; and healthy males showed a 20% decrease in postexercise plasma F₂-Isoprostanes following 28 days of supplementation with 20 mg MitoQ.¹⁹ A significant increase in plasma superoxide dismutase levels was observed after acute supplementation with MitoQ (80 mg) in patients with PAD.³⁰ Another study in healthy young adults found no changes in oxidative stress markers/antioxidant levels following MitoQ supplementation (20 mg/d for 21 days); however, exercise-induced nuclear and mitochondrial DNA damage decreased in lymphocytes and muscle following MitoQ.³⁷

Quantitative analyses conducted for oxidative stress-related outcomes reported in at least two studies found no significant effect of mitoAOX treatments on malondialdehyde or F₂-Isoprostanes (Table 3 and Figure S5).

3.4 | Adverse events and safety-related outcomes

Seventeen studies included in the review reported on adverse events and/or safety-related outcomes. Comparisons between mitoAOX and control groups in adverse event reports are shown in Table 4. There appeared to be no differences between mitoAOX and control treatments in the reviewed studies with respect to serious adverse events (SAEs), with only one study reporting one SAE in the Elamipretide arm causing participant discontinuation in the study,¹⁶ and one study reporting one SAE in the placebo arm causing myocardial infarction, death, and participant discontinuation in the study.³⁶ Non-serious treatment-emergent adverse events (TEAEs) tended to be higher with Elamipretide treatment compared with control when it was delivered by subcutaneous injection, largely because of increased mild-moderate injection site-related reactions such as injection site erythema, bruising, swelling and pruritis.^{16,17,32,36} One study reported a higher number of non-serious TEAEs with MitoQ versus control, because of increased gastrointestinal-related events such as nausea and vomiting.²⁵ However, this was not commonly reported across other studies.^{30,31,33} Discontinuation of participation because of TEAEs was minor, with only three studies reporting on a single participant withdrawing because of a TEAE.^{16,23,25} MitoAOX treatments had no apparent effect on all-cause mortality, CVD-related mortality, or health condition-related rehospitalizations versus control in the studies reviewed.^{16,17,22,26,36} Interestingly, mitoAOX treatments improved kidney function in some studies in patients with CVD-related impairments, as indicated by increases in the estimated glomerular filtration rate or an

attenuated rise in serum creatinine,^{24,26,34} although not in all studies.²² MitoQ supplementation at 40 and 80 mg/d also improved liver enzyme (aspartate aminotransferase, alanine aminotransferase) levels in one study in patients with a history of chronic hepatitis C virus infection.²⁵

4 | DISCUSSION

This systematic review evaluated current evidence from RCTs in humans on the effects of mitoAOXs on glycaemic control, cardiovascular health, and oxidative stress. The studies included were diverse with respect to target (clinical) population, specific study outcomes and the type of mitoAOX used. While our findings suggest limited evidence to support the use of mitoAOXs in the management of glycaemic control or cardiovascular health, there are some potentially promising findings that require further investigation. These findings include improved endothelial function (particularly brachial FMD) with mitoAOX supplementation in both healthy participants and in patients with specific health conditions; and improved blood pressure in patients with atherosclerosis-related impairment of renal blood flow. MitoQ also appeared to be effective in some studies to improve markers of oxidative stress, although the findings overall were mixed. In quantitative analyses, evidence certainty was rated as mostly low to very low across the study outcomes investigated.

Most studies that investigated the effects of Elamipretide involved patients with heart failure. Cardiac measures of global left ventricular systolic performance and remodelling such as LVESV, LVEDV, and LVEF were measured in some studies, with mixed findings reported. One study reported a dose-response-related effect of Elamipretide on LVESV and LVEDV,²³ which requires further investigation for a consensus on possible dose-related beneficial effects of Elamipretide in these patients. Based on findings from the small number of studies included in our review, there appears to be limited benefit of mitoAOXs on markers including E/e', early to late diastolic transmitral flow velocity ratio (E/a), LVGLS and NT-proBNP in patients with CVD.

Studies were also mixed with respect to improvements in functional capacity in patients with health conditions. However, one study did report a dose-related improvement in 6-minute walk test performance with Elamipretide in patients with primary mitochondrial myopathies.¹⁷ Future research needs to be conducted to further investigate possible dose-related effects of mitoAOX agents like Elamipretide on functional capacity-related outcomes in specific patient groups. With respect to patient-important adverse events, current evidence appears to suggest limited effects of mitoAOX agents on all-cause mortality, CVD-related mortality, incidence of new congestive heart failure, rehospitalization because of heart failure, and duration of hospitalization.^{16,17,22,26,36} However, the studies included in the review were mostly short term in duration, with a need for longer term follow-up studies to better investigate these outcomes.

There is a notable absence of evidence on the effects of mitoAOXs on glycaemic control in humans. There was no evidence that mitoAOXs improved glycaemic control outcomes such as fasting

glucose in healthy patients; however, it is unclear how they might affect glycaemic control in patients with impaired glucose metabolism such as type 2 diabetes. Given promising evidence for improvements in glucose intolerance and insulin resistance in preclinical trials with obese rodents using mitoAOXs,¹³⁻¹⁵ these findings highlight a clear gap in the literature that should be a focus in future studies.

Current evidence is also lacking overall on the effects of mitoAOXs on oxidative stress outcomes in humans. Some studies, particularly in healthy participants, found improvements in oxidative stress markers with MitoQ supplementation.^{19,30,31,33} However, overall, the limited evidence is not suggestive of benefits of mitoAOXs on systemic markers of oxidative stress such as malondialdehyde and F₂-Isoprostanes. Given the pathogenic factors of elevated mitochondrial ROS and oxidative stress in chronic diseases such as CVD and type 2 diabetes,³⁹ further investigation into the effects of mitoAOXs on mitochondrial ROS and oxidative stress markers is required in target clinical population groups.

Elamipretide and MitoQ appear to be well tolerated in participants, as indicated by a lack of SAEs and mostly mild-moderate TEAEs when they occurred.^{16,17,19,22-27,30-37} Non-serious TEAEs tended to be higher after subcutaneously injected (but not intravenously infused) Elamipretide because of an increase in injection site-related events such as pruritis, soreness, erythema and swelling.^{16,17,32,36} While this does appear to be a potential drawback to the practicality of this treatment, such adverse events only led to discontinuation of one participant across all the studies reviewed. Based on studies with multiple mitoAOX treatment doses, there did not appear to be any dose-related effects of Elamipretide or MitoQ on adverse events. It is important to highlight that while we did report on adverse events in the included studies, adverse events were not specified in the search criteria; and thus, this review is not comprehensive with respect to a review of the safety of mitoAOXs. Thus, future reviews are required to provide a more comprehensive review of the safety and adverse effects of mitoAOXs.

The limitations of the current study relate to the variable aspects of the studies included with respect to outcomes, study participants, mitoAOX agent used, and mitoAOX dosage considerations. The findings of quantitative comparisons undertaken should be regarded cautiously, because of factors such as the inclusion of only a small number of studies including specific outcomes, the combining of different mitoAOX agents together, the combining of different population groups together (i.e. patients with specific health conditions and healthy participants) and the combining of different mitoAOX treatment dosages together. There were insufficient studies for specific outcomes to undertake subgroup analyses to further investigate potential areas of participant and supplement heterogeneity. There was a notable absence of studies involving long-term supplementation with mitoAOX agents, with chronic supplementation studies lasting a median of 28 days (range 5-84 days). Thus, conclusions are limited to mostly short-term/acute mitoAOX treatments.

While some included studies did include functional/patient-important outcomes, mostly only surrogate outcomes were sufficiently measured across studies for quantitative analysis. While a strength of our systematic review is the inclusion of grey literature (conference abstracts/clinical trial registry data), some important

study-related data and outcome data might have been lacking from these data sources. Thus, there was possibly insufficient information available from those studies to allow for a comprehensive and accurate evaluation of risk of bias using the Cochrane risk of bias tool. Finally, we have only reviewed antioxidant compounds that are (by design) specific to mitochondria. It is probable that other, more generally acting antioxidants, have redox-related effects in mitochondria.⁴⁰ Thus, our review is not comprehensive with respect to all possible antioxidant compounds that have mitochondrial effects.

Overall, there is limited evidence from RCTs to support the use of mitoAOXs for management of glycaemic control and cardiovascular health in humans. There appears to be some potential for the use of mitoAOXs such as MitoQ for improving endothelial function; and future research should focus on the effects of MitoQ on endothelial function and glycaemic control in target clinical populations. At present, the diversity in studies with respect to participant population, outcomes measured, mitoAOX agent used, and dosage regimen used makes it difficult to draw clear conclusions with respect to specific antioxidant agent effectiveness and the most optimal target patient group and optimal dosage regimen.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

All named authors conceived the systematic review and were involved in preparation and critical revision of the manuscript. Shaun Mason and Lewan Parker performed systematic searches, study selections, data extractions and risk of bias analyses, with adjudications made by Glenn Wadley and Michelle Keske. Shaun Mason performed quantitative and qualitative data analyses and is guarantor of the work, taking responsibility for integrity and accuracy of the manuscript output.

PEER REVIEW

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14669>.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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